(12) PATENT
(19) AUSTRALIAN PATENT OFFICE

(11) Application No. AU 199713764 B2
(10) Patent No. 716665

(54) Title

Medicament intended to the treatment of obsessive compulsive troubles, sleep apnoea, sexual dysfunctions, emesa and transport sickness

(51)[6] International Patent Classification(s)
A61K 031/505 A61K 031/495

(21) Application No: 199713764 (22) Application Date: 1996.12.11

(87) WIPO No: WO97/21439

(30) Priority Data

(31) Number	(32) Date	(33) Country
95/14690	1995.12.12	FR

(43) Publication Date : 1997.07.03
(43) Publication Journal Date : 1997.08.28
(44) Accepted Journal Date : 2000.03.02

(71) Applicant(s)

Laboratorios Del Dr. Esteve, S.A.

(72) Inventor(s)

Jordi Frigola Constansa

(74) Agent/Attorney

PHILLIPS ORMONDE and FITZPATRICK,367 Collins Street,MELBOURNE VIC 3000

OPI DATE 03/07/97 APPLN. ID 13764/97
AOJP DATE 28/08/97 PCT NUMBER PCT/EP96/05736
AU9713764
DEMANDE

(51) Classification internationale des brevets 6 : A61K 31/505, 31/495

A1

(11) Numéro de publication internationale: WO 97/21439

(43) Date de publication internationale: 19 juin 1997 (19.06.97)

(21) Numéro de la demande internationale: PCT/EP96/05736

(22) Date de dépôt international: 11 décembre 1996 (11.12.96)

(30) Données relatives à la priorité:
95/14690 12 décembre 1995 (12.12.95) FR

(71) Déposant (*pour tous les Etats désignés sauf US*): LABORATORIOS DEL DR. ESTEVE, S.A. [ES/ES]; Avenida Mare de Deu de Montserrat, 221, E-08026 Barcelona (ES).

(72) Inventeur; et
(75) Inventeur/Déposant (*US seulement*): FRIGOLA-CONSTANSA, Jordi [ES/ES]; Avenida Diagonal, 299 at. 1a, E-08013 Barcelona (ES).

(74) Mandataires: MARTIN, Jean-Jacques etc.; Cabinet Régimbeau, 26, avenue Kléber, F-75116 Paris (FR).

(81) Etats désignés: AL, AM, AT, AU, AZ, BB, BG, BR, BY, CA, CH, CN, CU, CZ, DE, DK, EE, FI, GB, GE, HU, IL, IS, JP, KE, KG, KP, KR, KZ, LK, LR, LS, LT, LU, LV, MD, MG, MK, MN, MW, MX, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, TJ, TM, TR, TT, UA, UG, US, UZ, VN, brevet ARIPO (KE, LS, MW, SD, SZ, UG), brevet eurasien (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), brevet européen (AT, BE, CH, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), brevet OAPI (BF, BJ, CF, CG, CI, CM, GA, GN, ML, MR, NE, SN, TD, TG).

Publiée
Avec rapport de recherche internationale.
Avant l'expiration du délai prévu pour la modification des revendications, sera republiée si de telles modifications sont reçues.

(54) Title: MEDICAMENT INTENDED TO THE TREATMENT OF OBSESSIVE COMPULSIVE TROUBLES, SLEEP APNOEA, SEXUAL DYSFUNCTIONS, EMESA AND TRANSPORT SICKNESS

(54) Titre: MEDICAMENT DESTINE AU TRAITEMENT DES TROUBLES OBSESSIFS COMPULSIFS, DE L'APNEE DU SOMMEIL, DES DYSFONCTIONS SEXUELLES, DE L'EMESE ET DU MAL DES TRANSPORTS

(57) Abstract

The invention relates to the use of derivatives of 1-{4-[4-aryl(or heteroaryl)-1-piperazinyl]-butyl}-1H-azole, as well as physiologically acceptable salts thereof, for the fabrication of medicaments intented to the treatment of obsessive compulsive troubles, sleep apnoea, sexual dysfunctions, emesa and transport sickness.

(57) Abrégé

L'invention concerne l'utilisation des dérivés de 1-{4-[4-aryl(ou hétéroaryl)-1-pipérazinyl]-butyl}-1H-azole, ainsi que de leurs sels physiologiquement acceptables, pour la fabrication de médicaments destinés au traitement des troubles obsessifs compulsifs, de l'apnée du sommeil, des dysfonctions sexuelles, de l'émèse et du mal des transports.

PATENT

USE OF 1-{4-[4-ARYL (OR HETEROARYL)-1-PIPERAZINYL]BUTYL}-1H-AZOLE DERIVATIVES FOR THE PREPARATION OF A MEDICAMENT FOR USE IN THE TREATMENT OF COMPULSIVE OBSESSIVE DISORDERS, SLEEP APNOEA SYNDROME, SEXUAL DYSFUNCTIONS, EMESIS AND TRAVEL SICKNESS IN MAMMALS, INCLUDING MAN.

LABORATORIOS DEL DR. ESTEVE, S.A.

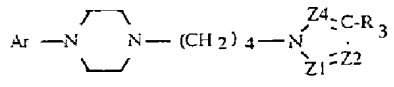
ABSTRACT

The invention relates to the use of 1-{4-[4-aryl (or heteroaryl)-1-piperazinyl]butyl}-1H-azole derivatives, as well as to their physiologically acceptable salts, for the manufacture of medicaments for use in the treatment of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis and travel sickness.

The present invention relates to the use of 1-{4-[4-aryl (or heteroaryl)-1-piperazinyl]butyl}-1H-azole derivatives, as well as to their physiologically acceptable salts, for the manufacture of medicaments for use in the treatment of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis and travel sickness.

The compounds to which the present invention relates have been described in European Patents EP-0,382,637 and EP-0,497,659, as well as in European Patent EP-0,502,786 which relates to a process for the preparation of aryl (or heteroaryl)-piperazinyl-butyl-azole derivatives. In Patents EP-0,382,637 and EP-0,497,659, we have claimed the use of these compounds for the treatment of certain diseases of the central nervous system. We have now discovered that aryl (or heteroaryl)-piperazinyl-butyl-azole derivatives show antiobsessive activity, activity towards preventing sleep apnoea syndrome, activity which facilitates sexual behaviour, and antiemetic and antinausea activity and they are consequently useful in therapy for the prevention and treatment of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions and nausea and vomiting induced, in particular, by cytotoxic radiotherapy and/or chemotherapy or movement. In particular, the compounds are for use in the preventive or curative treatment in man and animals of depression compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis and travel sickness.

The compounds recommended within the context of the present invention correspond to the general formula I



(I)

in which

Ar represents a nitrogenous or non-nitrogenous aromatic radical chosen from variously substituted aryls, variously substituted 2-pyrimidine, and 3-(1,2-benzisothiazole),

Z1 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_1,

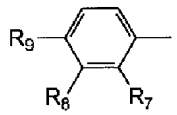
Z2 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_2,

Z4 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_4,

and R_1, R_2, R_3 and R_4, which are identical or different and may also form part of another aromatic or non-aromatic ring, represent a hydrogen atom, a halogen, a C_1-C_6 alkyl radical, a nitro radical, a hydroxyl radical, a C_1-C_6 alkoxy radical, a cyano radical, a hydroxycarbonyl radical, a C_1-C_6 alkoxycarbonyl radical, an aryl or substituted aryl radical, a sulphonic radical, a sulphonamido radical, an aminocarbonyl radical, which may or may not be substituted on the amino group, an amino or substituted amino radical,

and their therapeutically acceptable salts.

When Ar represents a variously substituted aryl, it is preferably a radical of formula



in which R_7, R_8 and R_9, which are identical or different, represent a hydrogen atom, a halogen, an alkyl radical, a perhaloalkyl radical, a hydroxyl radical, an alkoxy radical or a cyano radical.

According to the invention, the term alkyl is understood to refer to lower alkyls, preferably linear or branched, optionally unsaturated C_1-C_6 alkyls, in particular the methyl, ethyl, propyl, isopropyl, butyl, isobutyl, tert-butyl, pentyl and hexyl radicals and their various isomers. This definition also applies for the alkyl residues of the alkoxy radicals.

According to the present invention, the term halogen is preferably understood to refer to fluorine, chlorine, bromine or iodine.

According to the invention, the term aryl is understood to refer in particular to an aromatic or heteroaromatic radical chosen, in particular, from the phenyl, naphthyl, anthryl, phenanthryl, pyridyl, pyrimidyl, etc. radicals, preferably phenyl, optionally substituted, in particular with one or more radicals selected from halogens, lower alkyl, nitro, hydroxyl, alkoxy, cyano, hydroxycarbonyl, alkoxycarbonyl, aryl or substituted aryl, sulphonic and sulphonamido radicals, aminocarbonyl radicals, which are substituted or unsubstituted on the amino group, and amino or substituted amino radicals.

The substituents of the amino group are, in particular, alkyl or aryl radicals.

The term therapeutically acceptable salts is understood to refer to the usual salts of addition of organic or inorganic acids, such as the hydrochlorides, dihydrochlorides, mesylates or tosylates.

The compounds identified in Examples 1 to 84 below are obtained by the procedures described in Patents EP-0,382,637, EP-0,497,659 and EP-0,502,786, and the data for their identification are detailed in Table I.

EXAMPLES

1. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}pyrrole,
2. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}carbazole,
3. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}indole,
4. 2,3-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}indole,
5. 4-carboxamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
6. 4-carboxy-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
7. 3-methyl-5-trifluoromethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
8. 4,5-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-

butyl}-1H-imidazole,

9. 2,4,5-triphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,

10. 4,5-diphenyl-2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,

11. 4,5-dichloro-2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,

12. 2-ethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,

13. 2-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,

14. 4-methoxycarbonyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,

15. 4-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,

16. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-benzimidazole,

17. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-3H-imidazo[5,4-b]pyridine,

18. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazo[4,5-b]pyridine,

19. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-benzotriazole,

20. 2-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,

21. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-1,2,4-triazole,

22. 2-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-2H-benzotriazole,

23. 2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,

24. 5,6-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,

25. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,

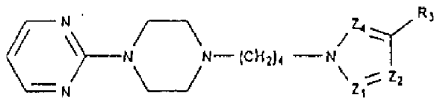
26. 3,5-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,

27. 3,5-dimethyl-4-nitro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
28. 4-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
29. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
30. 4-bromo-3,5-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
31. 4-nitro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
32. 4-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole dihydrochloride,
33. 4-ethoxycarbonyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
34. 3-methyl-5-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
35. 4-bromo-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
36. 4-cyano-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
37. 4-fluoro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
38. 4-amino-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
39. 4-methylsulphonamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
40. 4-benzamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
41. 4-acetamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
42. 4-(2-butyl)amino-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
43. 3-chloro-4-fluoro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
44. 4-(4-methoxyphenyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
45. 4-(4-chlorophenyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,

46. 4-(1-pyrrolyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
47. 4-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
48. 3,5-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
49. 4-phenylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
50. 4-(4-methylbenzene)sulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
51. 4-butylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
52. 4-propylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
53. 4-ethylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
54. 3,5-dimethyl-4-(N,N-dimethylsulphonamido)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
55. 4-N-methylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
56. 4-sulphonic-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
57. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1-imidazole,
58. 2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
59. 4,5-dichloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
60. 4-chloro-1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
61. 4,5-dichloro-2-methyl-1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]butyl}-1H-imidazole,
62. 4-chloro-1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
63. 4,5-dichloro-2-methyl-1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}-1H-imidazole,
64. 4-chloro-1-{4-[4-(3-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,

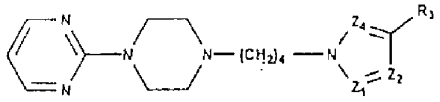
65. 1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]butyl}pyrrole,
66. 1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}pyrrole,
67. 1-{4-[4-(phenyl)-1-piperazinyl]butyl}pyrrole,
68. 4-chloro-1-{4-[4-(phenyl)-1-piperazinyl]butyl}-1H-pyrazole,
69. 4,5-dichloro-2-methyl-1-{4-[4-(phenyl)-1-piperazinyl]butyl}-1H-imidazole,
70. 4-chloro-1-{4-[4-(2-chlorophenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
71. 4,5-dichloro-2-methyl-1-{4-[4-(2-chlorophenyl)-1-piperazinyl]butyl}-1H-imidazole,
72. 4-chloro-1-{4-[4-(3-chlorophenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
73. 4,5-dichloro-2-methyl-1-{4-[4-(2-cyanophenyl)-1-piperazinyl]butyl}-1H-imidazole,
74. 4,5-dichloro-2-methyl-1-{4-[4-(2-fluorophenyl)-1-piperazinyl]butyl}-1H-imidazole,
75. 4-chloro-1-{4-[4-(2-cyanophenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
76. 4,5-dichloro-2-methyl-1-{4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl}-1H-imidazole,
77. 4-chloro-1-{4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl}-1H-pyrazole,
78. 4-chloro-1-{4-[4-(2-fluorophenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
79. 4-chloro-1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-pyrazole,
80. 4,5-dichloro-2-methyl-1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-imidazole,
81. 1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-butyl}-1H-1,2,4-triazole,
82. 1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]-butyl}-1H-benzimidazole,
83. 4-bromo-1-{4-[4-(5-bromopyrimidin-2-yl)-1-piperazinyl]butyl}-1H-pyrazole,
84. 4-chloro-{4-[4-(5-bromopyrimidin-2-yl)-1-piperazinyl]butyl}-1H-pyrazole.

TABLE I



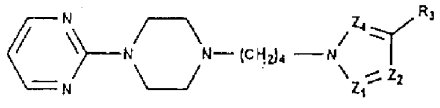
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
1	CH	CH	CH	H	oil	2941, 1585, 1547, 1500, 1360, 1260, 983, 724 (film)	$CDCl_3$	1.55 (m, 2H); 1.77 (m, 2H); 2.25-2.55 (a.c. 6H); 3.70-4,05 (a.c. 6H); 6.13 (t, J=2, OHz, 2H); 6.47 (t, J=4, 7Hz, 1H); 6.65 (t, J=2, OHz, 2H); 8.29 (d, J=4 ,7Hz, 2H)
2	C-CH=CH-CH=CH-C		C-CH=CH-CH=CH-		oil	2941, 1586, 1547, 1511, 1484, 1402, 1359, 1307, 1260, 983, 750, 723 (film)	$CDCl_3$	1,6 (m, 2H); 1,86 (m, 2H); 2,27-2,45 (a.c. 6H); 3,78 (t, J=5, 2Hz, 4H); 4,30 (t, J=7, 1Hz, 2H); 6,43 (t, J=4, 7Hz, 1H); 7.12-7,46 (a.c. 6H); 8,07 (d, J=6, 5Hz, 2H); 8,26 (d, J=4, 7Hz, 2H)
3	C-CH=CH-CH=CH-C		CH	H	oil	2940, 1585, 1547, 1510, 1446, 1359, 1259, 983, 741 (film)	$CDCl_3$	1,54 (m, 2H); 1,88 (m, 2H); 2,37 (a.c. 6H); 3,79 (t, J=5Hz, 4H), 4,13 (t, J=6, 8Hz, 2H); 6.45 (a.c. 2H); 6,9-7.1 (a.c. 5H); 8.27 (d, J=4, 7Hz, 2H)

TABLE I (continued)



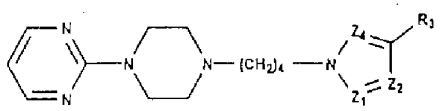
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
4	C-CH=CH-CH=CH-C		CPh	Ph	oil	2942, 1586, 1547, 1502, 1447, 1359, 1261, 984, 789, 757, 702 (film)	$CDCl_3$	1,38 (m, 2H); 1,68 (m, 2H); 2,10-2,40 (a.c. 6H); 3.76 (t, J=5Hz, 4H); 4,11 (t, J=7Hz, 2H); 6,41 (t, J=4, 7Hz, 1H); 7.10-7.50 (a.c. 13H); 7.79 (m, 1H); 8.25 (d, J=4, 7Hz, 2H)
5	N	CH	CH	$-\overset{O}{\overset{\|}{C}}-NH_2$	124°C	3337, 3156, 1663, 1601, 1586, 1446, 1360, 980 (KBr)	DMSO-d_6	1,38 (m, 2H); 1,81 (m, 2H); 2.3-2,5 (a.c. 6H); 3.69 (m, 4H); 4,14 (t, J=7Hz, 2H); 6,6 (t, J=4, 7Hz, 1H); 7.0 (broad , 1H); 7,7 (broad , 1H); 7,89 (s, 1H); 8,24 (s, 1H); 8,35(d, J=4, 6Hz, 2H)
6	N	CH	CH	$-\overset{O}{\overset{\|}{C}}-OH$	104-105°C	3100, 2943, 1602, 1587, 1546, 1487, 1440, 1360, 1260, 797 (film)	DMSO-d_6	1.40 (m, 2H); 1,81 (m, 2H); 2,23-2,49 (a.c. 6H); 3,0 (broad , 1H); 3,64 (m, 4H); 4.13 (t ,J=7Hz, 2H); 6,6 (t, J=4, 7Hz, 1H); 7,7 (s, 1H); 8,1 (s, 1H); 8.33 (d, J=4, 7Hz, 2H)

TABLE I (continued)



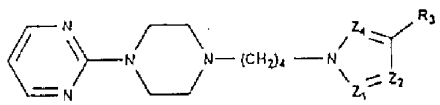
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
7	N	CMe	CCF_3	H	71-75°C	2937, 2856, 1586, 1544, 1496, 1393, 1228, 1177, 1125, 981 (KBr)	$CDCl_3$	1.57 (m, 2H); 1.89 (m, 2H); 2.32 (s, 3H); 2.30-2.55 (a.c. 6H); 3.82 (t, J=5Hz, 4H); 4.10 (t, J=7Hz, 2H); 6.25 (s, 1H); 6.47 (t, J=4, 7Hz, 1H); 8.29 (d, J=4, 7Hz, 2H)
8	CH	N	CPh	Ph	Oil	2942, 1585, 1547, 1505, 1445, 1360, 1307, 1260, 983, 774, 754, 700 (film)	$CDCl_3$	1.55 (m, 4H); 2.16-2.42 (a.c. 6H); 3.71-3.89 (a.c. 6H); 6.47 (t, J=4, 7Hz, 1H); 7.12-7.60 (a.c. 11H); 8.27 (d, J=4, 7Hz, 2H)
9	CPh	N	CPh	Ph	oil	2942, 1585, 1546, 1501, 1445, 1360, 1260, 983, 698 (film)	$CDCl_3$	1.55 (m, 4H); 1.95-2.33 (a.c. 6H); 3.69-4.07 (a.c. 6H); 6.47 (t, J=4, 7Hz, 1H); 7.13-7.67 (a.c. 15H); 8.26 (d, J=4, 7Hz, 2H)

TABLE I (continued)



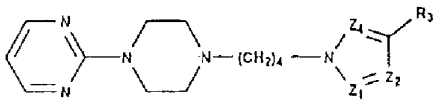
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
10	CMe	N	CPh	Ph	Oil	2942, 1585, 1547, 1500, 1446, 1393, 1260, 983, 760, 698 (film)	$CDCl_3$	1.43 (m, 4H); 2.18-2.47 (a.c. 9H); 3.72-3.76 (a.c. 6H); 6.47 (t, J=4, 7Hz, 1H); 7.09-7.39 (a.c. 10H); 8.26 (d, J=4, 7Hz, 2H)
11	CMe	N	CCl	Cl	oil	2942, 1586, 1547, 1500, 1447, 1359, 1259, 1245, 983 (film)	$CDCl_3$	1.45-1.84 (a.c. 4H); 2.26-2.57 (a.c. 9H); 3.74-4.05 (a.c. 6H); 6.48 (t, J=4, 7Hz, 1H); 8.30 (d, J=4, 7Hz, 2H)
12	CEt	N	CH	H	oil	2938, 1585, 1547, 1495, 1446, 1360, 1260, 983, 638 (film)	$CDCl_3$	1.34 (t, J=7, 1, 3H); 1.66 (m, 4H); 2.31-2.72 (a.c. 8H); 3.77-3.92 (a.c. 6H); 6.47 (t, J=4, 7Hz, 1H); 6.87 (d, J=10Hz, 2H); 8.26 (d, J=4, 7Hz, 2H)

TABLE I (continued)



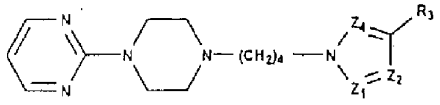
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR(100 MHz), δ, J=Hz
13	CPh	N	CH	H	Oil	2941, 1585, 1547, 1500, 1446, 1360, 1260, 983, 774, 700 (film)	$CDCl_3$	1.45 (m, 2H); 1.73 (m, 2H); 2.19-2.42 (a.c. 6H); 3.77 (t, J=5, 1Hz, 4H); 4.01 (t, J=7, 3Hz, 2H); 6.47 (t, J=4, 7Hz, 1H); 6.94-7.61 (a.c. 7H); 8.27 (d, J=4, 7Hz, 2H)
14	CH	N	CH		92-94°C	2800, 1713, 1585, 1544, 1483, 1360, 1223, 1117, 985 (KBr)	$CDCl_3$	1.45 (m, 2H); 1.72 (m, 2H); 2.29-2.39 (a.c. 6H); 3.65-3.74 (a.c. 7H); 4.01 (t, J=6, 8Hz, 2H); 6.47 (t, J=4, 7Hz, 1H); 7.67 (s, 1H); 7.81 (s, 1H); 8.24 (d, J=4, 7Hz, 2H)
15	CH	N	CH	Ph	105-107°C	2944, 1585, 1548, 1500, 1447, 1360, 1260, 983 (KBr)	DMSO-d_6	1.45 (m, 2H); 1.73 (m, 2H); 2.21-2.45 (a.c. 6H); 3.60-3.75 (a.c. 4H); 4.03 (t, J=6, 8Hz, 2H); 6.47 (t, J=4, 7Hz, 1H); 7.21-7.79 (a.c. 7H); 8.25 (d, J=4, 7Hz, 2H)

TABLE I (continued)



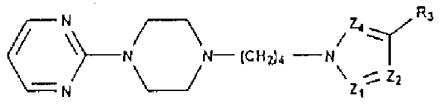
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
16	CH	N	C-CH=CH-CH=CH-		85-88°C	2944, 1581, 1542, 1488, 1466, 1355, 1259, 741 (KBr)	DMSO-d_6	1.40 (m, 2H); 1.82 (m, 2H); 2,26-2,42 (a.c. 6H); 3,62-3,71 (a.c. 4H); 4.24 (t, J=6, 9Hz, 2H); 6.56 (t, J=4, 7Hz, 1H); 7.16-7.26 (a.c. 2H); 7.55-7,70 (a.c. 2H); 8.22-8.34 (a.c. 3H)
17	CH	N	C-N=CH-CH=CH-		104°C	2935, 1578, 1545, 1482, 1443, 1409, 1357, 1256, 982, 751 (KBr)	DMSO-d_6	1,45 (m, 2H); 1.90 (m, 2H); 2,23-2,50 (a.c. 6H); 3,6 (t, J=4, 8Hz, 4H); 4,3 (t, J=7, 0Hz, 2H); 6,5 (t, J=4, 7Hz, 1H); 7.25 (d.d, J=4, 7Hz, 1H); 8.05 (d, J=7, 9Hz, 1H); 8.30-8,48 (a.c. 4H)
18	CH	N	C-CH=CH-CH=N-		134°C	2944, 2828, 1609, 1582, 1543, 1487, 1460, 1355, 1260, 982, 800 (KBr)	DMSO-d_6	1.42 (m, 2H); 1.84 (m, 2H); 2,28-2,49 (a.c. 6H); 3,60-3,69 (a.c. 4H); 4.03 (t, J=7, 0Hz, 2H); 6.5 (t, J=4, 7Hz, 1H); 7.28 (dd, J=4, 7Hz, 1H); 8,07 (d, J=7, 9Hz, 1H); 8,29-8,50 (a.c. 4H)

TABLE I (continued)



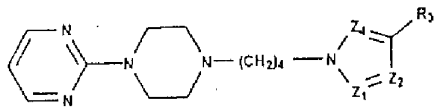
Example	Z_1	Z_2	Z_4	R_3	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
19	N	N	C-CH=CH-CH=CH-		89-90,5° C	2940, 2818, 1590, 1544, 1498, 1360, 1259, 984, 749 (KBr)	DMSO-d_6	1.43 (m, 2H); 1.97 (m, 2H); 2.24-2,53 (a.c. 6H); 3.66 (t, J=5, 1Hz, 4H); 4.75 (t, J=6, 8Hz, 2H); 6.60 (t, J=4, 7Hz, 1H); 7,52 (m, 2H); 8.01 (m, 2H); 8,31 (s, 1H); 8.36 (s, 1H)
20	CCl	N	C-CH=CH-CH=CH-		153-145°C	2940, 1583, 1542, 1491, 1466, 1443, 1383, 1264, 1128, 981, 742 (KBr)	DMSO-d_6	1.50 (m, 2H); 1.81 (m, 2H); 2,20-2,42 (a.c. 6H); 3,67 (m, 4H); 4,28 (t, J=7Hz, 2H); 6.58 (t, J=4, 7Hz, 1H); 7.30 (m, 2H); 7,60 (m, 2H); 8,31 (d, J=4, 7Hz, 2H)

TABLE I (continued)



Example	Z_1	Z_4	R_3	Z_2	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR 100 MHz), δ, J=Hz
21	CH	N	H	N	69-71°C	2942, 1582, 1546, 1458, 1448, 1360, 1261, 1138, 1011, 983, 680 (KBr)	$CDCl_3$	1,55 (m, 2H); 1.96 (m, 2H); 2.32-2.51 (a.c. 6H); 3.81 (t, J=5, 1Hz, 4H); 4.21 (t, J=7, 0Hz, 2H); 6.47 (t, J=4, 7Hz, 1H); 7.95 (s, 1H); 8.09 (s, 1H); 8.29 (d, J=4, 7Hz, 2H)
22	N	N	-CH=CH-CH=CH-C		97,4-98,2°C	2946, 2863, 2823, 1585, 1547, 1483, 1358, 1256, 982, 799, 761 (KBr)	DMSO-d_6	1,34-1.56 (m, 2H); 1,97-2.13 ((m, 2H); 2,18-2,48 (a.c. 6H); 3,65 (t, J=5, 3Hz, 4H); 4.75 (t, J=6, 8Hz, 2H); 6,56 (t, J=4, 7Hz, 1H); 7.40 (dd, J=6, 5Hz, J'=3, 1Hz, 2H); 7,90 (dd., J=6, 6Hz, J'=3, 3Hz, 2H); 8.28 (s, 1H); 8,33 (s, 1H)

TABLE I (continued)



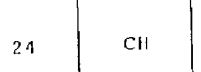
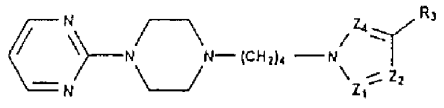
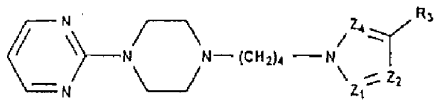
Example	Z_1	Z_4	R_3	Z_2	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
23	CMe	C-CH=CH-CH=CH-		N	101-102°C	2938, 2820, 1583, 1542, 1494, 1405, 1357, 1258, 983, 798, 744 (KBr)	$CDCl_3$	1,56-1.93 (a.c. 4H); 2,30-2,47 (a.c. 6H); 2,58 (s, 3H); 3,79 (t, J=5, 2Hz, 4H); 4,10 (t, J=7, 3Hz, 2H); 6,43 (t, J=4, 7Hz, 1H); 7.22 (m, 3H); 7,67 (m, 1H); 8.26 (d, J=4, 7Hz, 2H)
24	CH			N	105-106°C	2946, 1584, 1542, 1491, 1466, 1362, 1262, 983, 800, 742 (KBr)	$CDCl_3$	1,50 (m, 2H); 1,85 (m, 2H); 2.25-2,43 (a.c. 12H); 3,76 (t, J=5, 0Hz, 4H); 4,07 (t, J=7, 0Hz, 2H); 6,40 (t, J=4, 7Hz, 1H); 7.11 (s, 1H); 7.51 (s, 1H); 7,71 (s, 1H); 8,23 (d, J=4, 7Hz, 2H)

TABLE I (continued)



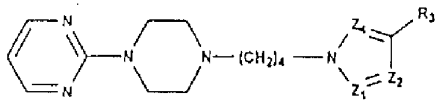
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
25	N	CH	H	CH	Oil	2942, 2815, 1586, 1547, 983 (film)	$CDCl_3$	1.50 (m, 2H); 1.90 (m, 2H); 2.40 (m, 6H); 3.80 (m, 4H); 4.12 (t, 2H, J=6, 9); 6.20 (t, 1H, J=1, 6); 6.40 (t, 1H, J=4, 7); 7.42 (dd, 2H, J=4, 7; J'=1.6); 8.25 (d, 2H, J=4, 7)
26	N	CMe	H	CMe	Oil	1590, 1550, 1350, 1260, 980 (film)	$CDCl_3$	1.58 (m, 2H); 1.85 (m, 2H); 2.20 (s, 3H); 2.25 (s, 3H); 2.44 (m, 6H); 3.81 (m, 4H); 3.97 (t, 2H, J=7, 2); 5.78 (s, 1H); 6.43 (t, 1H, J=4, 7); 8.27(d, 2H, J=4, 7)
27	N	CMe	NO_2	CMe	Oil	1590, 1550, 1350, 1260, 980 (film)	$CDCl_3$	1.60 (m, 2H); 1.90 (m, 2H); 2.49 (m, 9H); 2.63 (s, 3H); 3.82 (m, 4H); 4.09 (t, 2H, J=7); 6.48 (t, 1H ,J=4, 7); 8.29 (d, 2H, J=4, 7)

TABLE I (continued)



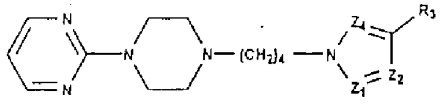
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
28	N	CH	Me	CH	Oil	1590, 1550, 1500, 1360, 1260, 980 (film)	$CDCl_3$	1.52 (m, 2H); 1.95 (m, 2H); 2.05 (s, 3H); 2.37 (m, 6H); 3.81 (m, 4H); 4.05 (t, 2H, J=6, 8); 6.41 (t, 1H, J=4, 7); 7.13 (s, 1H); 7.27 (s, 1H); 8.25 (d, 2H, J=4, 7)
29	N	CH	-CH=CH-CH=CH-C-		oil	2930, 1590, 1550, 1500, 1360, 1310, 1260, 980 (film)	$CDCl_3$	1.51 (m, 2H); 1.98 (m, 2H); 2.36 (m, 6H); 3.77 (m, 4H); 4.39 (t, 2H, J=6, 9); 6.40 (t, 1H, J=4, 7); 7.0-7.7 (m, 4H); 7.95 (s, 1H); 8.25 (d, 2H, J=4, 7)
30	N	CMe	Br	CMe	oil	2930, 1590, 1550, 1500, 1360, 1310, 1260, 980 (film)	$CDCl_3$	1.55 (m, 2H); 1.81 (m, 2H); 2.18 (s, 3H); 2.20 (s, 3H); 2.38 (m, 4H); 3.80 (m, 4H); 3.99 (t, 2H, J=6, 9); 6.42 (t, 1H, J=4, 7); 8.25 (d, 2H, J=4, 7)

TABLE I (continued)



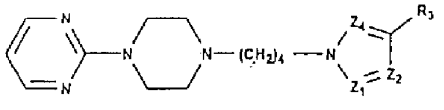
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
31	N	CH	NO_2	CH	94-96°C	1584, 1524, 1480, 1444, 1406, 1359, 1305, 819, (KBr)	$CDCl_3$	1.5 (m, 2H); 1.93 (m, 2H); 2.38 (m, 6H); 3.76 (m, 4H); 4.15 (t, 2H, J=6, 7); 6.42 (t, 1H, J=4, 7); 8.01 (s, 1H); 8.12 (s, 1H); 8.24 (d, 2H, J=4, 7)
32	N	CH	Cl	CH	2 HCl 195-8°C	3429, 2688, 1636, 1620, 1346, 1218, 971	DMSO-d_6	1.69 (m, 2H); 1.81 (m, 2H); 2.98 (m, 2H); 3.08 (m, 2H); 3.39-3.53 (m, 4H); 4.12 (t, 2H); 4.67 (d, 2H); 6.77 (t, 1H); 7.53 (d, 1H); 8.04 (d, 1H); 8.45 (d, 2H)
33	N	CH	EtOOC-	CH	Oil	1715, 1586, 1222, 983 (film)	$CDCl_3$	1.34 (t, 3H, J=7.1); 1.54 (m, 2H); 1.90 (m, 2H); 2.46 (m, 6H); 3.81 (m, 4H); 4.25 (m, 4H); 6.47 (t, 1H, J=4, 7); 7.90 (s, 2H); 8.29 (d, 2H, J=4, 7)

TABLE I (continued)



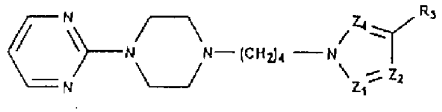
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
34	N	CMe	H	CPh	Oil	1586, 1547, 1360, 983 (film)	$CDCl_3$	1.54 (m, 2H); 1.85 (m, 2H); 2.28 (s, 3H); 2.45 (m, 6H); 3.81 (m, 4H); 4.07 (t, 2H, J=7); 6.28 (s, 1H); 6.43 (t, 1H, J=4, 7); 7.33 (m, 4H); 7.75 (m, 2H); 8.26 (d, 2H, J=4, 7)
35	N	CH	Br	CH	oil	1586, 1547, 1360, 984 (film)	$CDCl_3$	1.52 (m, 2H); 1.89 (m, 2H); 2.44 (m, 6H); 3.62 (m, 4H); 4.11 (t, 2H, J=6, 7); 6.46 (t, 1H, J=4, 6); 7.42 (s, 1H); 7.45 (s, 1H); 8.29 (d, 2H, J=4, 6)
36	N	CH	C≡N	CH	94-95°C	3076, 2231, 1587, 1551, 1258, 982 (KBr)	$CDCl_3$	1.54 (m, 2H); 1.96 (m, 2H); 2.40 (m, 6H); 3.81 (m, 4H); 4.20 (t, 2H, J=6, 9); 6.48 (t, 1H, J=4, 7); 7.80 (s, 1H); 7.83 (s, 1H); 8.29 (d, 2H, J=4, 7)

TABLE I (continued)



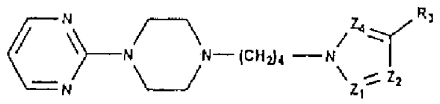
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR(100 MHz), δ, J=Hz
37	N	CH	F	CH	Oil	2944, 1584, 1546, 1507, 1359, 1260, 983 (film)	$CDCl_3$	1.45 (m, 2H); 1.96 (m, 2H); 2.36 (m, 6H); 3.77 (m, 4H); 4.0 (t, 2H, J=6, 9); 6.47 (t, 1H, J=4, 7); 7.27 (m, 2H, J=4, 8); 8.29 (d, 2H, J=4, 8)
38	CH	CH	H_2N-	N	oil	1586, 1548, 1360, 984 (film)	$CDCl_3$	1.50 (m, 2H); 1.85 (m, 2H); 2.43 (m, 6H); 3.4 (élargie 2H); 3.8 (m, 6H); 4.0 (t, 2H, J=6, 4); 6.46 (t, 1H, J=4, 7); 6.98 (s, 1H); 7.10 (s, 1H); 8.27 (d, 2H, J=4, 7)
39	CH	CH	Me-SO_2-NH-	N	132°C	1582, 1482, 1360, 1150, 983 (KBr)	$CDCl_3$	1.58 (m, 2H); 1.93 (m, 2H); 2.45 (m, 6H); 2.94 (s, 3H); 3.8 (m, 4H); 4.11 (t, 2H, J=6, 9); 6.45 (t, 1H, J=4, 7); 7.4 (s, 1H); 7.5 (s, 1H); 8.28 (d, 2H, J=4, 7)

TABLE I (continued)



Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
40	CH	CH	Ph-CO-NH-	N	134-136°C	1646, 1586, 1542, 1369 (KBr)	$CDCl_3$	1.55 (m, 2H); 1.79 (s, 3H); 1.88 (m, 2H); 2.42 (m, 6H); 3.80 (m, 4H); 4.13 (t, 2H, J=6, 8); 6.51 (t, 1H, J=4, 7); 7.49 (m, 4H); 7.83 (m, 2H); 8.0 (s, 1H); 8.11 (s, 1H); 8.28 (d, 2H, J=4, 7)
41	CH	CH	Me-CO-NH-	N	80-82°C	1650, 1586, 1454, 1364, 1261, 983 (KBr)	$CDCl_3$	1.50 (m, 2H); 1.88 (m, 2H); 2.11 (s, 3H); 2.43 (m, 6H); 3,79 (m, 4H); 4.8 (t, 2H, J=6, 8); 6.47 (t, 1H, J=4, 7); 7.36 (s, 1H); 7.93 (s, 1H); 8.28 (d, 2H, J=4 ,6); 9.25 (s, 1H)

TABLE I (continued)



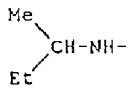
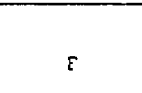
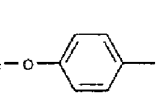
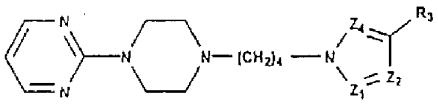
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR (100 MHz), δ, J=Hz
42	CH	CH		N	Oil	2960, 1585, 1547, 1359, 1260, 983 (film)	$CDCl_3$	1.00 (t, 3H, J=7, 0); 1.19 (d, 3H, J=6, 3); 1.6 (m, 4H); 1.90 (m, 2H); 2.50 (m, 6H); 3.0 (m, 3H); 3.9 (m, 4H); 4.1 (t, 2H, J=6, 8); 6,52 (t, 1H, J=4, 7); 6,99 (s, 1H); 7.17 (s, 1H); 3.37 (d, 2H, J=4, 7))
43	N	CCl		CH	Oil	2944, 1585, 1547, 1507, 1360, 1260, 984 (film)	$CDCl_3$	1.52 (m, 2H); 1.90 (m, 2H); 2.40 (m, 6H); 3.80 (m, 4H); 4.0 (t, 2H, J=4, 8); 6.45 (t, 1H, J=4, 7); 7.30 (d, 1H, J=4, 8); 8.29 (d ,2H, J=4.8)
44	N	CH		CH	79-82°C	2390, 1589, 1545, 1495, 1360, 1247, 983, 835, 799 (KBr)	$CDCl_3$	1.62 (m, 2H); 1,88 (m, 2H); 2.45 (m, 6H); 3.81 (m, 7H); 4.16 (t, 2H, J=6, 8); 6.46 (t, 1H, J=4, 7); 6,9 (d, 2H, J=4, 4); 7.4 (d, 2H, J=4, 4); 7.55 (s, 1H); 7,7 (s, 1H); 8.28 (d, 2H, J=2, 4)

TABLE I (continued)



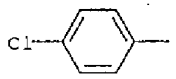
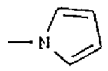
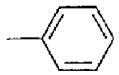
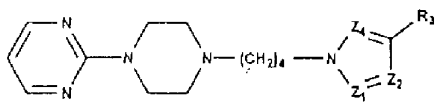
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR (100 MHz), δ, J=Hz
45	N	CH		CH	108-110°C	2946, 1586, 1549, 1485, 1395, 1257, 982, 951, 830 (KBr)	$CDCl_3$	1.6 (m, 2H); 1.9 (m, 2H); 2.46 (m, 6H); 3.8 (m, 4H); 4.16 (t, 2H, J=6, 8); 6.4 (t, 1H, J=4, 7); 7.36 (d, 4H, J=1, 3); 7.7 (d, 2H, J=6, 2); 8.28 (d, 2H, J=2, 3)
46	N	CH		CH	Oil	2943, 1586, 1487, 1359, 1260, 984, 726 (film)	$CDCl_3$	1.55 (m, 2H); 1.80 (m, 2H); 2.45 (m, 6H); 3.81 (t, 4H, J=5); 4.12 (t, 2H, J=7); 6.25 (2H, t, J=2); 6.44 (1H, t, J=4, 7); 6.84 (m, 2H); 7.5 (d, 2H, J=5); 8.27 (d, 2H, J=4, 7)
47	N	CH		CH	39-42°C	2942, 1585, 1493, 1446, 1359, 1258, 983, 760 (film)	$CDCl_3$	1.6 (m, 2H); 1.9 (m, 2H); 2.5 (m, 4H); 3.8 (m, 6H); 4.2 (t, 2H, J=6, 8); 6.7 (t, 1H, J=4, 7); 7.2-7.7 (ams. compl. 5H); 8.0 (s, 1H); 8.2 (s, 1H); 8.4 (d, 2H, J=2, 3)

TABLE I (continued)



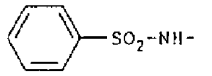
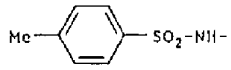
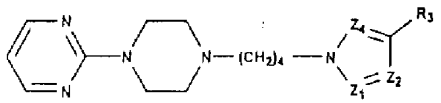
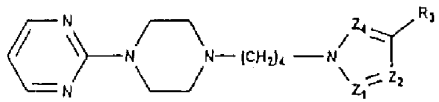
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
48	N	CPh	H	CPh	80-82°C	2942, 1585, 1547, 1485, 1359, 1260, 983, 763, 697 (film)	$CDCl_3$	1.6 (m, 2H); 1.9 (m, 2H); 2.35 (m, 6H); 3.8 (m, 4H); 4.2 (t, 2H, J=6, 8); 6.4 (t, 1H, J=4, 7); 6.6 (s, 1H); 7.2-7.4 (abs. compl. 8H); 7.8 (m, 2H); 8.25 (d, 2H, J=2, 4)
49	N	CH		CH	92-95°C	2931, 1584, 1548, 1490, 1358, 1167, 983 (KBr)	$CDCl_3$	1.45 (m, 2H); 1.85 (m, 2H); 2.40 (m, 6H); 3.80 (m, 4H); 4.0 (t, 2H, J=6, 7); 6.47 (t, 1H, J=4, 6); 7.0 (s, 1H); 7.5 (m, 6H); 8.3 (d, 2H, 2 J=4, 6)
50	N	CH		CH	108-110°C	2943, 1585, 1548, 1446, 1360, 1161, 984 (KBr)	$CDCl_3$	1.5 (m, 2H); 1.85 (m, 2H); 2.28 (m, 9H); 3.8 (m, 4H); 4.0 (m, 2H); 6.45 (t, 1H, J=4, 7); 7-7.65 (m, 6H); 8.27 (d, 2H, J=4, 7)

TABLE I (continued)



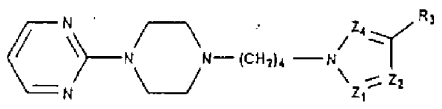
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
51	N	CH	n-Bu-SO_2-NH-	CH	Oil	2941, 1586, 1548, 1448, 1360, 1146, 984, 755 (film)	$CDCl_3$	0.91 (t, 3H, J=6, 8); 1.45 (m, 4H); 1.85 (m, 4H); 2.40 (m, 6H); 3.0 (m, 2H); 3.80 (m, 4H); 4.11 (t, 2H, J=6, 5); 6,5 (t, 1H, J=4, 7); 7.4 (m, 2H); 7.5 (s, 1H); 8.3 (d, 2H, J=4, 7)
52	N	CH	n-Pr-SO_2-NH-	CH	Oil	2940, 1586, 1548, 1447, 1360, 1146, 984, 755 (film)	$CDCl_3$	1.0 (t, 3H, J=7, 1); 1.55 (m, 2H); 1,9 (m, 4H); 2,45 (m, 6H); 3.0 (t, 2H, J=7, 4); 3.8 (m, 4H); 4,1 (t, 2H, J=6, 4); 6,46 (t, 1H, J=4, 7); 7.35 (m, 2H); 7.5 (s, 1H); 8.3 (d, 2H, J=4, 7)
53	N	CH	Et-SO_2-NH-	CH	oil	2943, 1586, 1548, 1447, 1360, 1146, 984, 754 (film)	$CDCl_3$	1.36 (m, 5H); 1.9 (m, 2H); 2.45 (m, 6H); 3.0 (m, 2H); 3.6 (m, 4H); 4,1 (t, 2H, J=6, 4); 6.45 (t, 1H, J=4, 7); 7.39 (s, 1H); 7.51 (s, 1H); 8.3 (d, 2H, J=4, 7)

TABLE I (continued)



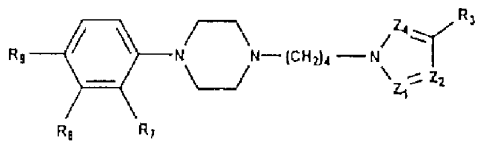
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR (100 MHz), δ, J=Hz
54	N	CMe	$-SO_2-N-Me_2$	CMe	Oil	2939, 1586, 1547, 1448, 1360, 1290, 983, 951, 788 (film)	$CDCl_3$	1.7 (m, 4H); 2.3-3,0 (abs. compl. 18H); 3.8 (m, 4H); 4.0 (t, 2H, J=6, 8); 6.5 (t, 1H, J=4, 7); 8.2 (d, 2H, J=2, 35)
55	N	CH	$-SO_2-N-Me_2$	CH	100-102°C	3135, 2943, 1586, 1512, 1357, 1328, 1156, 982, 728 (KBr)	$CDCl_3$	1.6 (m, 2H); 1.9 (m, 2H); 2,3-2,7 (abs. compl. 13H); 3,8 (m, 4H); 4.2 (t, 2H, J=6, 8); 6,4 (t, 1H, J=4, 7); 7,75 (d, 1H, J=4, 4); 8,28 (d, 2H, J=2, 4)
56	N	CH	$-SO_3-H$	CH	230-235°C	3330, 1590, 1556, 1449, 1220, 1178, 1049, 971, 656 (KBr)	D_2O	1,95 (m, 2H); 3,3 (m, 6H); 4,0 (s, 5H); 4,27 (t, 2H, J=6, 1); 6.8 (t, 1H, J=4, 8); 7.8 (s, 1H); 8.0 (s, 1H); 8,43 (d, 2H, J=2, 4)
57	CH	N	H	CH	oil	2940, 1585, 1500, 1360, 1260, 975 (film)	$CDCl_3$	1,6 (m, 2H); 1.8 (m, 2H); 2,5 (m, 6H); 3,80 (m, 6H); 6,5 (t, 1H, J=4, 7); 6,9 (s, 1H); 7,1 (s, 1H); 7,5 (s, 1H); 8,4 (d, 2H, J=4, 7)

TABLE I (continued)



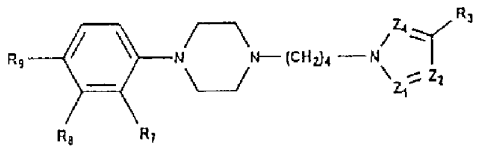
Example	Z_1	Z_2	R_3	Z_4	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
58	CMe	N	H	CH	Oil	2941, 1586, 1547, 1499, 1359, 1259, 983 (film)	$CDCl_3$	1.72 (m, 4H); 2.37 (s, 3H); 2.44 (m, 6H); 3.80 (m, 6H); 6.45 (t, 1H, J=4, 7); 6.85 (d, 2H, J=4, 5); 8.27 (d, 2H, J=4, 7)
59	CH	N	Cl	CCl	69-71°C	2946, 1584, 1543, 1492, 1359, 1254, 983, 797 (KBr)	$CDCl_3$	1.4-2.1 (abs.compl. 4H); 2.46 (m, 6H); 3.86 (m, 6H); 6.47 (t, 1H, J=4, 7); 7.38 (s, 1H); 8.29 (d, 2H, J=4, 7)

TABLE I (continued)



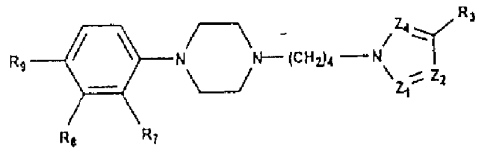
Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
60	N	CH	Cl	CH	H	H	MeO-	76-77°C	2833, 1511, 1448, 1247, 1029, 979, 824 (KBr)	DMSO-d_6	1.43 (m, 2H); 1.78 (m, 2H); 1.71-2.48 (a.c. 6H); 2.93-3.02 (m, 4H); 3.67 (s, 3H); 4.09 (t, J=6, 8Hz, 2H); 6.83 (s, 4H); 7.52 (s, 1H); 7.98 (s, 1H)
61	CMe	N	Cl	CCl	H	H	MeO-	73-75°C	2940, 2818, 1512, 1457, 1245, 1183, 1036, 826 (KBr)	DMSO-d_6	1.33-1.87 (a.c. 4H); 2.32 (s, 3H); 2.41-2.51 (a.c. 6H); 2.82-3.0 (m, 4H); 3.67 (s, 3H); 3.93 (t, J=7, 2Hz, 2H); 6.83 (s, 4H);
62	N	CH	Cl	CH	MeO-	H	H	Oil	2941, 2816, 1500, 1450, 1241, 749 (film)	DMSO-d_6	1.39 (m, 2H); 1.77 (m, 2H); 2.22-2.45 (a.c. 6H); 2.92 (m, 4H); 3.76 (s, 3H); 4.07 (t, J=6, 0Hz, 2H); 6.87 (m, 4H); 7.51 (s. 1H); 7.95 (s, 1H)

TABLE I (continued)



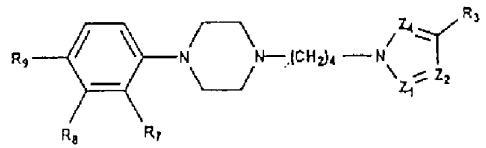
Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR(100 MHz), δ, J=Hz
63	CMe	N	Cl	CCl	MeO-	H	H	82-83°C	2943, 2820, 1502, 1405, 1241, 1030, 746 (KBr)	DMSO-d_6	1.43-1.60 (a.c. 4H); 2.33 (s, 3H); 2.40-2.50 (a.c. 6H); 2.95 (m, 4H); 3.76 (s, 3H); 3.93 (t, J=7, 0Hz, 2H); 6.89 (m, 4H)
64	N	CH	Cl	CH	H	MeO-	H	Oil	2943, 2820, 1601, 1578, 1496, 1451, 1203, 1171, 970 (film)	$CDCl_3$	1.52 (m, 2H); 1.85 (m, 2H); 2,28-2.56 (a.c. 6H); 3,16 (m, 4H); 3.7 (s, 3H); 4.05 (t, J=7, 0Hz, 2H); 6.4 (m, 3H); 7.15 (m, 1H); 7.34 (s, 1H); 7.40 (s, 1H)
65	CH	CH	H	CH	H	H	MeO-	oil	2943, 2815, 1512, 1455, 1244, 1037, 823, 724 (film)	$CDCl_3$	1.50-1.80 (a.c. 4H); 2.31-2,61 (a.c. 6H); 3,06 (m, 4H); 3.74 (s, 3H); 3.81 (t, J=7, 0Hz, 2H); 6.1 (m, 2H); 6,6 (m, 2H); 6,04 (s, 4H)

TABLE I (continued)



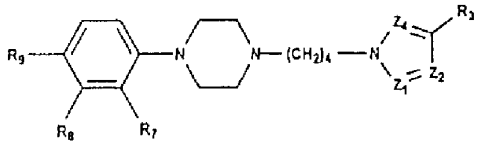
Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
66	CH	CH	H	CH	MeO-	H	H	Oil	2940, 2814, 1500, 1451, 1281, 1241, 1028, 743, 723 (film)	$CDCl_3$	1,50-1,85 (a.c. 4H); 2,33-2,66 (a.c. 6H); 3,10 (m, 4H); 3,84-3,96 (a.c. 5H); 6,12 (t, J=2Hz, 2H); 6,65 (t, J=2Hz, 2H); 6,93 (m, 4H)
67	CH	CH	H	CH	H	H	H	oil	2943, 2817, 1600, 1501, 1235, 759, 723, 692 (film)	$CDCl_3$	1.41-1.89 (a.c. 4H); 2.37 (t, J=7, 3Hz, 2H); 2.50-2.60 (a.c. 4H); 3,18 (m, 4H); 3.89 (t, J=6, 9Hz, 2H); 6.13 (t, J=2, 0Hz, 2H); 6.64 (t, J=2, 0Hz, 2H); 6,83-7.33 (a.c. 5H)

TABLE I (continued)



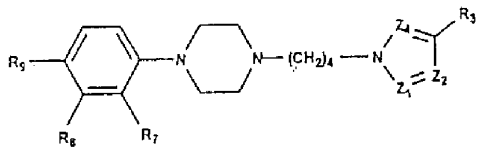
Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR(100 MHz), δ, J=Hz
68	N	CH	Cl	CH	H	H	H	58-61°C	2942, 2819, 1600, 1500, 1450, 1381, 1311, 1240, 1140, 966, 756 (KBr)	$CDCl_3$	1.47 (m, 2H); 1.84 (m, 2H); 2.35 (t, J=7, 2Hz, 2H); 2.52 (m, 4H); 3.16 (m, 4H); 4.04 (t, J=6, 8Hz, 2H); 6.75-6.94 a.c. 3H); 7.16 (s, H); 7.23 (s, 1H); 7.35 (d, J=7, 4Hz, 2H)
69	CMe	N	Cl	CCl	H	H	H	Oil	2944, 2819, 1600, 1532, 1503, 1453, 1404, 1244, 1143, 759, 692 (film)	$CDCl_3$	1.43-1.87 (a.c. 4H); 2.33 (s, 3H); 2.38-2.60 (a.c. 6H); 3.17 (m, H); 3.83 (t, J=7Hz, 2H); 6.9 (a.c. 3H); 7.24 (m, 2H)
70	N	CH	CH	CH	Cl	H	H	oil	2943, 2817, 1587, 1480, 1443, 1231, 1040, 971, 751, 612 (film)	$DMSO-d_6$	1.40 (m, 2H); 1.78 (m, 2H); 2.2-2,6 (a.c. 6H); 2.95 (m, 4H); 4.08 (t, J=6, 5Hz, 2H); 6.95-7.41 (a.c. 4H); 7.50 (s, 1H); 7.97 (s, 1H)

TABLE I (continued)



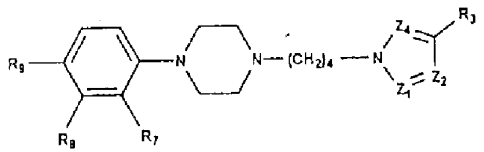
Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR (100 MHz), δ, J=Hz
71	CMe	N	Cl	CCl	Cl	H	H	89-91°C	2936, 2818, 1587, 1531, 1480, 1359, 1243, 1229, 1036, 1016, (KBr)	$CDCl_3$	1,3-1,8 (a.c., 4H); 2,32 (s, 3H); 2,35-2,70 (a.c. 6H); 2,96 (m, 4H); 3,94 (t, J=7, 2Hz, 2H); 6,90-7,50 (a.c. aH)
72	N	CH	Cl	CH	H	Cl	H	Oil	2944, 2820, 1594, 1564, 1487, 1451, 1433, 1384, 1239, 987, 980 (film)	$CDCl_3$	1.3-1,70 (m, 2H); 1,70-2,10 (m, 2H); 2.39 (t, J=7, 4Hz, 2H); 2.59 (m, 4H); 3,17 (m, 4H); 4.09 (t, J=4Hz, 2H); 6,6-6,9 (a.c. 3H); 7.15 (t, J=8, OHz, 1H); 7.37 (s, 1H); 7.4 (s, 1H)
73	CMe	N	Cl	CCl	CN	H	H	80° (Dec)	2956, 2848, 2219, 1593, 1488, 1240, 1232, 1010, 765 (KBr)	$CDCl_3$	1.45-1.80 (a.c. 4H); 2,37 (s, 3H): 2,20-2.70 (a.c. 6H); 3.23 (m, 4H); 3.88 (t, J=7, 1Hz, 2H); 6,90-7,06 (a.c. 2H); 7,30-7.60 (a.c. 2H)

TABLE I (continued)



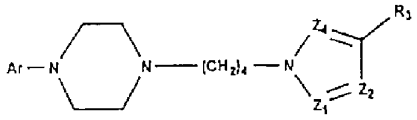
Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR(100 MHz), δ, J=Hz
74	CMe	N	Cl	CCl	F	H	H	Oil	2944, 2822, 1501, 1406, 1241, 1141, 754 (film)	$CDCl_3$	1.30-1,80 (a.c., 4H); 2.35 (s, 3H); 2.20-2.70 (a.c. 6H); 3.10 (m, 4H); 3.87 (t, J=7Hz, 2H); 6.70-7.07 (a.c. 4H)
75	N	CH	Cl	CH	CN	H	H	59° (dec)	2948, 2823, 2219, 1596, 1488, 1447, 1376, 1231, 971, 762 (film)	$CDCl_3$	1.50 (m, 2H); 1.86 (m, 2H); 2.43 (t, J=7Hz, 2H); 2.63 (m, 4H); 3.23 (m, 4H); 4.11 (t, J=6, 8Hz, 2H); 6.80-7.10 (a.c. 2H); 7.25-7.65 (a.c. 4H)
76	CMe	N	Cl	CCl	H	CF_3	H	oil	2946, 2821, 1609, 1450, 1357, 1319, 1245, 1163, 1122, 697 (film)	$CDCl_3$	1.35-1.75 (a.c. 4H); 2,35 (s, 3H); 2.30-2.65 (a.c. 6H); 3.22 (m, 4H); 3.87 (t, J=7, 1Hz, 2H); 6.95-7.10 (a.c. 3H); 7.32 (m, 1H)

TABLE I (continued)



Example	Z_1	Z_2	R_3	Z_4	R_7	R_8	R_9	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR(100 MHz), δ, J=Hz
77	N	CH	Cl	CH	H	CF_3	H	Oil	2947, 2821, 1610, 1450, 1357, 1319, 1163, 1123, 696 (film)	$CDCl_3$	1.49 (m, 2H); 1.89 (m, 2H); 2.38 (t, J=7, 2Hz, 2H); 2.53 (m, 4H); 3.21 (m, 4H); 4.08 (t, J=6, 8Hz, 2H); 6.95-7.12 (a.c. 3H); 7.20-7.45 (m, 3H[δ = 7.36 s ,1H; δ =7.40 s, 1H])
78	N	CH	Cl	CH	F	H	H	oil	2944, 2820, 1501, 1451, 1239, 971, 753 (film)	$CDCl_3$	1,50 (m, 2H); 1,89 (m, 2H); 2,41 (t, J=7, 2Hz, 2H); 2,59 (m, 4H); 3,10 (m, 4H); 4,09 (t, J=6, 9Hz); 6,80-7,10 (a.c. 4H); 7,37 (s, 1H); 7,40 (s, 1H);

TABLE I (continued)



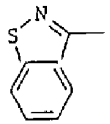
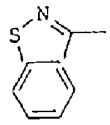
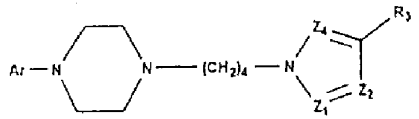
Example	Z_1	Z_2	Z_4	R_3	Ar	m.p.	IR cm^{-1}	NMR solvent	^1H-NMR(100 MHz), δ, J=Hz
79	N	CH	CH	Cl		Oil	2943, 2815, 1493, 1451, 1423, 1383, 1307, 1261, 970, 739, 613 (film)	$CDCl_3$	1.50 (m, 2H); 1.85 (m, 2H); 2.45 (t, J=7, 2Hz, 2H); 2.60 (t, J=4, 7Hz, 4H); 3.53 (t, J=5, 0Hz, 4H); 4.07 (t, J=7, 0Hz, 2H); 7.35 (m, 4H); 7.85 (m, 2H)
80	CMe	N	CCl	Cl		oil	2944, 2816, 1533, 1493, 1422, 1380, 1280, 1246, 1139, 1017, 754, 665 (film)	$CDCl_3$	1.55-1.85 (a.c. 4H); 2.34-2.49 (a.c. 5H); 2.62 (t, J=4, 7Hz, 4H); 3.53 (t, J=5, 0Hz, 4H); 3.84 (t, J=7, 0Hz, 2H); 7.37 (m, 2H); 7.83 (m, 2H)

TABLE I (continued)



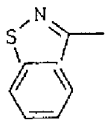
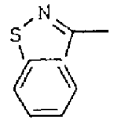
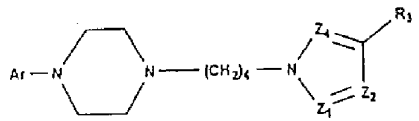
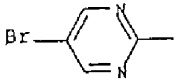
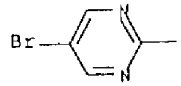
Example	Z_1	Z_2	Z_4	R_3	Ar	m.p.	IR cm^{-1}	NMR solvent	^{1}H-NMR (100 MHz), δ, J=Hz
81	CH	N	N	H		102-4°C	2943, 2809, 1493, 1426, 1275, 1152, 1007, 738, 678	$CDCl_3$	1,55 (m, 2H); 1.97 (m, 2H); 2,45 (t, J=7, 3 2H); 2,64 (a.c. 4H); 3,55 (a.c. 4H); 4.22 (t, J=6, 9Hz, 2H); 7,35 (m, 1H); 7.46 (m, 1H); 7.80 (d, J=8Hz, 1H); 7,90 (d, J=8Hz, 1H); 7.95 (s, 1H); 8.08 (s, 1H)
82	CH	N	C-CH=CH-CH=CH			Oil	2944, 2828, 1495, 1459, 1422, 1285, 746 (film)	$CDCl_3$	1.56 (m, 2H); 1,96 (m, 2H); 2.42 (t, J=7, 1Hz, 2H); 2,61 (a.c. 4H); 3,53 (a.c. 4H); 4.19 (t, J=7, 0Hz, 2H); 7.10-7.50 (a.c. 5H); 7.70-7.90 (a.c. 4H)

TABLE I (continued)



Example	Z_1	Z_2	Z_4	R_3	Ar	m.p.	IR cm^{-1}	NMR · solvent	^{1}H-NMR(100 MHz), δ, J=Hz
83	N	CH	CH	Br		84,6°C	2952, 1583, 1526, 1365, 1311, 950 (KBr)	$CDCl_3$	1.57 (m, 2H); 1.90 (m, 2H); 2.45 (m, 6H); 3.80 (t, 4H, J=6, 8); 7.44 (d, 2H, J=4); 8.29 (s, 2H)
84	N	CH	CH	Cl		85-86°C	1585, 1525, 1495, 1364 (KBr)	$CDCl_3$	1.50 (m, 2H); 1.86 (m, 2H); 2.40 (m, 6H); 3.76 (m, 4H); 4.08 (m, 2H); 7.4 (t, 2H, J=6, 9); 8.25 (s, 2H)

The examples which follow illustrate the properties of a few derivatives which fall within the scope of the present invention.

I. COMPULSIVE OBSESSIVE DISORDER

Given that serotonin (5-HT) is believed to be involved in the pathophysiology of affective disorders, pharmacological stimulation paradigms have largely been used to determine the "in vivo" dynamics of the function of serotonin in compulsive obsessive disorder, inter alia. The 5-HT precursors (α-tryptophan and 5-hydroxytryptophan), the 5-HT uptake inhibitors and/or liberators (DL-fenfluramine) and the agonists which act directly on 5-HT (m-CPP, MK-212 and buspirone) have attracted considerable attention as possible probes of the functional state of the central nervous system of 5-HT in several affective disorders, although both the specificity for the 5-HT system in general and the selectivity for the 5-HT receptor subtypes in particular continue to be contested (*Murphy et al.: J. Clin. Psychiatry 47: 9-15, 1986; Murphy et al.: Br. K. Psychiatry 155 (suppl. 8): 15-24, 1989; Van de Kar, S.D.: Neurosci. Biobehav. Rev. 13: 237-246, 1989*).

Moreover, there is increasing evidence that the 5-HT_{1A} ligands buspirone, gepirone and ipsapirone are anxiolytic active agents, possibly with antiobsessive properties, although their mechanism of action is not very clear (*Lesch et al.: Life Sci. 46: 1271-1277, 1990*).

During the study of the anxiolytic activity of agents with affinity for the 5-HT_{1A} receptor, one of the most representative tests is that which determines the avoidance behaviour of mice in a box with a very brightly lit compartment, light box, and the other dark (light/dark box) (*Costall et al.: J. Pharmacol. Exp. Ther. 262 (1): 90-98, 1992*).

The mice are placed in the lit compartment which becomes their aversion and provokes in them a state of anxiety. This provokes a fleeing reaction towards the dark compartment, which may be associated with compulsive

obsessive behaviour. The results obtained (see table) demonstrate that lesopitron, at all the test doses, delays the appearance of the compulsive obsessive behaviour of movement to the dark area since the delay time increases clearly.

Treatment	Delay in passing from lit area to dark area
Controls (vehicle)	10 seconds
Lesopitron 0.0001 mg/kg, ip	15 seconds
Lesopitron 0.01 mg/kg, ip	20 seconds
Lesopitron 0.5 mg/kg, ip	24 seconds

II. SLEEP APNOEA SYNDROME

Sleep apnoea syndrome comprises a series of disorders of different gravity. Sleep apnoea is classified as obstructive, central or mixed, depending on the presence or absence of respiratory efforts during periods in which the airflow is stopped. Obstructive and mixed apnoeas are the most common. They exhibit the syndrome of obstructive sleep apnoea, in which recurrent and sporadic collapses of the upper respiratory pathways are observed during sleep. If the collapse is complete, there is no circulation of air through the nose and the mouth, and respiration stops. The usual result is partial wakening from sleep and a return to normal respiration. In several cases, the patient does not remember these episodes of apnoea, but he feels tired and sleepy during the day, for no apparent reason. These episodes of recurrent apnoea with hypoxaemia and fragmented sleep may lead to serious neurological and heart consequences.

Hitherto, the pharmacological treatment of sleep apnoea syndrome has met with little success. Recently, a few publications have reported the possible usefulnes of buspirone, a 5-HT_{1A} agonist, in sleep apnoea disorders (*Mendelson et al., J. Clin. Psychopharmacol. 1991 11 (1):71*).

In order to determine the action of lesopitron on

respiration and sleep, and consequently the possible use of this agent in sleep apnoea syndrome, its effect was studied on the respiration of rats, following the work carried out in this respect on buspirone (*Mendelson et al., Am. Rev. Respir. Dis. 14(6): 1527-1530, 1990*).

The results obtained demonstrate that at doses of 10 and 30 mg/kg, i.v., lesopitron gives rise to a significant increase in the breathing rate, as well as to pulmonary ventilation in anaesthetized rats.

Respiratory action of lesopitron on rats anaesthetized with uretane.

Lesopitron dose (mg/kg, i.v.)	Pulmonary ventilation (increase maxima)	Increase in the breathing rate (inhalations/ minute
0.3	10 %	9
1	20 %	15
3	20 %	18
10	22 %	20
30	44 %	23

The electroencephalographic study of the rats' sleep demonstrated that at 5 mg/kg lesopitron significantly increases the sleep latency at the same time as it decreases the total sleeping time, that is to say that it increases the period of wakefulness.

Electroencephalographic study of sleep in rats.

Group	Sleep latency (min)		Period of wakefulness (min)
	no REM	REM	
Control (vehicle)	32 ± 3	62 ± 6	90 ± 5
Lesopitron (5 mg/kg, s.c.)	71 ± 4 (*)	194 ± 14(*)	130 ± 4 (*)

Summarizing the results obtained, it may be affirmed that lesopitron may be a respiratory stimulant with persistent effects during sleep. It is consequently indicated in the treatment of sleep apnoea syndrome.

III <u>SEXUAL DYSFUNCTION</u>

The aetiology of sexual dysfunction may include psychological factors, interpersonal and circumstantial reasons, physical factors and also secondary effects of

pharmacological agents.

Given that sexual dysfunction may be due to a wide variety of these underlying causes, which may range from those which are purely psychogenic to entirely physical causes, it would not be realistic to hope that a single mode of treatment could become effective in all cases. In the usual clinical practices, sexual dysfunction is treated by determining the underlying causes and by treating them whenever possible. In several cases, identification of the underlying causes of sexual dysfunction in men and women is very complex, or even, it cannot be determined with certainty. The psychopharmacological treatment of sexual dysfunction is currently in its infancy. The use of medicaments to treat sexual dysfunction has met with little success, which is demonstrated by the absence of a treatment which is widely accepted and recognized for this use.

Activation of the 5-HT_{1A} receptors appears to facilitate the sexual behaviour of male rats, given that 8-OH-DPAT increases the number of sexual encounters and decreases the ejaculation latency (*Murphy et el.: J. Clin. Psychiatry 47: 9-15, 1986; Murphy et al.: Br. K. Psychiatry 155 (suppl. 8): 15-24, 1989*). Similar effects have been found with other 5-HT_{1A} receptor-selective products such as buspirone, gepirone or ipsapirone. However, it is not known if the effect of 5-HT_{1A} agonists in the sexual behaviour of male and female rats is provoked, either by stimulation of the 5-HT_{1A} auto-receptors by these products - this reduces the synthesis of 5-HT and causes the serotoninergic function to decrease - or by stimulation of the post-synaptically localized receptors.

In order to demonstrate the capacity of lesopitron to improve sexual dysfunction, its action on the sexual behaviour of male rats was evaluated. In this respect, the methodology described by M.M. Foreman et al. (*J. Pharmacol. Exp. Ther. 270 (3): 1270-1281 (1994)*) was followed. The main indicator used to evaluate the action of the product was the EL (time required to reach

ejaculation, or ejaculation latency after intromission).

Dose of lesopitron (mg/kg, subcutaneous)	% inhibition in ejaculation latency (EL)* relative to the control group
0.1	40 %
1	60 %
10	70 %

* EL for the group treated with vehicle: 745 ± 30 seconds

The results obtained with lesopitron demonstrate the activity of the product in facilitating the sexual behaviour of rats.

IV. **EMESIS**

The compounds of the invention were studied with regard to their effects on emesis in ferrets according to a method described by Costall et al. (*Neuropharmacology, 1986, 25, 959-961*).

Ferrets of both sexes (0.7 - 1.4 kg) were caged individually at 21 ± 1°C and were fed normally. The compound of Example 32 or a vehicle was then administered to them subcutaneously as a pretreatment of 15 minutes before the administration of cisplatin (10 mg/kg i.v. via a fixed jugular cannula). The animals were observed at the start of the emesis and afterwards, for 240 minutes. The emesis was characterized by rhythmic abdominal contractions, either associated with the expulsion of solid or liquid matter (that is to say vomiting) or not associated with the passage of matter through the mouth (nausea). The number of episodes and the nausea or the vomiting were recorded.

The compound of Example 32 is capable of antagonizing the emesis induced by cisplatin (Figure 1).

Figure 1: The compound of Example 32 is capable of antagonizing the emesis induced by cisplatin in fer-

rets. The animals received a vehicle (V, n = 7) or the compound of Example 32 (0.05 - 0.5 mg/kg s.c., n = 4) for each level of dose, 15 minutes before the intravenous administration of cisplatin (10 mg/kg). The animals were observed for 240 minutes. A significant difference when compared with V is indicated $^{s}P < 0.05$ (Mann-Whitney U test).

In human therapy, the dose of administration is obviously a function of the seriousness of the complaint to be treated. It will generally be between about 5 and about 100 mg/day. The derivatives of the invention will be administered, for example, in the form of tablets or gelatin capsules or alternatively intravenously. Two specific pharmaceutical forms are shown below, by way of example.

Example of a tablet formulation

Compound of Example 32	20 mg
Lactose	50 mg
Microcrystalline cellulose	20 mg
Povidone	5 mg
Pregelatinized starch	3 mg
Colloidal silica dioxide	1 mg
Magnesium stearate	1 mg
Tablet weight	100 mg

Example of a gelatin capsule formulation

Compound of Example 32	20 mg
Polyoxyethylenated glycerol	125 mg
Glyceryl behenate	5 mg
	150 mg

Excipient: soft gelatin q.s.

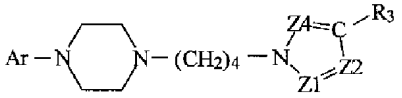
Example of an injection ampule formulation

Compound of Example 32	4 mg	8 mg
Sodium chloride	15 mg	30 mg
Water for injection q.s.	2 ml	4 ml

Given the advantageous pharmacological properties associated with the compounds of general formula I, the present invention covers the use of these compounds as medicaments, the pharmaceutical compositions containing them and their use for the manufacture of medicaments for use in the treatment of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis and travel sickness, in particular for the manufacture of antiobsessive agents, agents for preventing sleep apnoea syndrome, agents which facilitate sexual behaviour, and antiemetic and antinausea agents.

THE CLAIMS DEFINING THE INVENTION ARE AS FOLLOWS:

1. Use of compounds of general formula I



in which

Ar represents a nitrogenous or non-nitrogenous aromatic radical chosen from variously substituted aryls, variously substituted 2-pyrimidine, and 3-(1,2-benzisothiazole),

Z1 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_1,

Z2 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_2,

Z4 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_4,

and R_1, R_2, R_3 and R_4, which are identical or different and may also form part of another aromatic or non-aromatic ring, represent a hydrogen atom, a halogen, a C_1-C_6 alkyl (as hereinbefore defined) radical, a nitro radical, a hydroxyl radical, a C_1-C_6 alkoxy radical (as hereinbefore defined), a cyano radical, a hydroxycarbonyl radical, a C_1-C_6 alkoxycarbonyl radical, an aryl or substituted aryl radical, a sulphonic radical, a sulphonamido radical, an aminocarbonyl radical, which may or may not be substituted on the amino group, an amino or substituted amino radical,

and their therapeutically acceptable salts,

for the preparation of a medicament for use in the treatment of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis induced by cisplatin and travel sickness in mammals, including man.

2. Use according to Claim 1, wherein the compounds of general formula I are selected from the following group:

1. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}pyrrole,
2. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}carbazole,

3. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}indole,
4. 2,3-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}indole,
5. 4-carboxamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
6. 4-carboxy-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
7. 3-methyl-5-trifluoromethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
8. 4,5-diphenyl-1-{4-[4-(2-pyrimidinyl)piperazinyl]-butyl}-1H-imidazole,
9. 2,4,5-triphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
10. 4,5-diphenyl-2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
11. 4,5-dichloro-2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
12. 2-ethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
13. 2-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
14. 4-methoxycarbonyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
15. 4-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
16. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-benzimidazole,
17. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-3H-imidazo[5,4-b]pyridine,
18. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazo[4,5-b]pyridine,
19. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-benzotriazole,
20. 2-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benz. nidazole,
21. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-1,2,4-triazole,
22. 2-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-2H-benzotriazole,

23. 2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,
24. 5,6-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,
25. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
26. 3,5-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
27. 3,5-dimethyl-4-nitro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
28. 4-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
29. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
30. 4-bromo-3,5-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
31. 4-nitro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
32. 4-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole dihydrochloride,
33. 4-ethoxycarbonyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
34. 3-methyl-5-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
35. 4-bromo-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
36. 4-cyano-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
37. 4-fluoro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
38. 4-amino-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
39. 4-methylsulphonamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
40. 4-benzamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
41. 4-acetamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,

42. 4-(2-butyl)amino-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
43. 3-chloro-4-fluoro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
44. 4-(4-methoxyphenyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
45. 4-(4-chlorophenyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
46. 4-(1-pyrrolyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
47. 4-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
48. 3,5-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
49. 4-phenylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
50. 4-(4-methylbenzene)sulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
51. 4-butylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
52. 4-propylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
53. 4-ethylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
54. 3,5-dimethyl-4-(N,N-dimethylsulphonamido)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
55. 4-N-methylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
56. 4-sulphonic-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
57. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1-imidazole,
58. 2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
59. 4,5-dichloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
60. 4-chloro-1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,

61. 4,5-dichloro-2-methyl-1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]butyl}-1H-imidazole,
62. 4-chloro-1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
63. 4,5-dichloro-2-methyl-1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}-1H-imidazole,
64. 4-chloro-1-{4-[4-(3-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
65. 1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]butyl}pyrrole,
66. 1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}pyrrole,
67. 1-{4-[4-(phenyl)-1-piperazinyl]butyl}pyrrole,
68. 4-chloro-1-{4-[4-(phenyl)-1-piperazinyl]butyl}-1H-pyrazole,
69. 4,5-dichloro-2-methyl-1-{4-[4-(phenyl)-1-piperazinyl]butyl}-1H-imidazole,
70. 4-chloro-1-{4-[4-(2-chlorophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
71. 4,5-dichloro-2-methyl-1-{4-[4-(2-chlorophenyl)-1-piperazinyl]butyl}-1H-imidazole,
72. 4-chloro-1-{4-[4-(3-chlorophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
73. 4,5-dichloro-2-methyl-1-{4-[4-(2-cyanophenyl)-1-piperazinyl]butyl}-1H-imidazole,
74. 4,5-dichloro-2-methyl-1-{4-[4-(2-fluorophenyl)-1-piperazinyl]butyl}-1H-imidazole,
75. 4-chloro-1-{4-[4-(2-cyanophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
76. 4,5-dichloro-2-methyl-1-{4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl}-1H-imidazole,
77. 4-chloro-1-{4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl}-1H-pyrazole,
78. 4-chloro-1-{4-[4-(2-fluorophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
79. 4-chloro-1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-pyrazole,
80. 4,5-dichloro-2-methyl-1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-imidazole,

81. 1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-1,2,4-triazole,

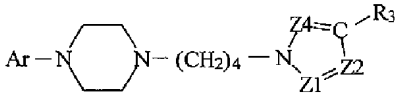
82. 1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-benzimidazole,

83. 4-bromo-1-{4-[4-(5-bromopyrimidin-2-yl)-1-piperazinyl]butyl}-1H-pyrazole,

84. 4-chloro-{4-[4-(5-bromopyrimidin-2-yl)-1-piperazinyl]butyl}-1H-pyrazole.

3. Use of 4-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole dihydrochloride for the preparation of a medicament for use in the treatment of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis induced by cisplatin and travel sickness in mammals, including man.

4. Method of treatment of a condition selected from the group consisting of compulsive obsessive disorders, sleep apnoea syndrome, sexual dysfunctions, emesis induced by cisplatin and travel sickness in a mammal including administration of a therapeutically effective amount of a compound of general formula I



in which

Ar represents a nitrogenous or non-nitrogenous aromatic radical chosen from variously substituted aryls, variously substituted 2-pyrimidine, and 3-(1,2-benzisothiazole),

Z1 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_1,

Z2 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_2,

Z4 represents a nitrogen atom or a substituted or unsubstituted carbon atom which may be represented by: C-R_4,

and R_1, R_2, R_3 and R_4, which are identical or different and may also form part of another aromatic or non-aromatic ring, represent a hydrogen atom, a halogen, a C_1-C_6 alkyl (as hereinbefore defined) radical, a nitro radical, a hydroxyl radical, a C_1-C_6 alkoxy radical (as hereinbefore defined), a cyano radical, a hydroxycarbonyl radical, a C_1-C_6 alkoxycarbonyl radical, an aryl or substituted aryl radical, a sulphonic radical, a sulphonamido radical, an

aminocarbonyl radical, which may or may not be substituted on the amino group, an amino or substituted amino radical,

or a therapeutically acceptable salt thereof to said mammal.

5. A method according to claim 4 wherein said condition is compulsive obsessive disorder.

6. A method according to claim 4 wherein said condition is sleep apnoea syndrome.

7. A method according to claim 4 wherein said condition is sexual dysfunction.

8. A method according to claim 4 wherein said condition is emesis.

9. A method according to claim 4 wherein said condition is travel sickness.

10. A method according to any one of claims 4-9 wherein said compound of general formula I is selected from the group:

1. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}pyrrole,

2. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}carbazole,

3. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}indole,
4. 2,3-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}indole,
5. 4-carboxamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
6. 4-carboxy-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
7. 3-methyl-5-trifluoromethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
8. 4,5-diphenyl-1-{4-[4-(2-pyrimidinyl)piperazinyl]-butyl}-1H-imidazole,
9. 2,4,5-triphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
10. 4,5-diphenyl-2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
11. 4,5-dichloro-2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
12. 2-ethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
13. 2-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
14. 4-methoxycarbonyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
15. 4-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
16. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-benzimidazole,
17. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-3H-imidazo[5,4-b]pyridine,
18. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazo[4,5-b]pyridine,
19. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-benzotriazole,
20. 2-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benz. nidazole,
21. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-1,2,4-triazole,
22. 2-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-2H-benzotriazole,

23. 2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,
24. 5,6-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-benzimidazole,
25. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
26. 3,5-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
27. 3,5-dimethyl-4-nitro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
28. 4-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
29. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-imidazole,
30. 4-bromo-3,5-dimethyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
31. 4-nitro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
32. 4-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole dihydrochloride,
33. 4-ethoxycarbonyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
34. 3-methyl-5-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
35. 4-bromo-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
36. 4-cyano-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
37. 4-fluoro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
38. 4-amino-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
39. 4-methylsulphonamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
40. 4-benzamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
41. 4-acetamido-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,

42. 4-(2-butyl)amino-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
43. 3-chloro-4-fluoro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
44. 4-(4-methoxyphenyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
45. 4-(4-chlorophenyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
46. 4-(1-pyrrolyl)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
47. 4-phenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
48. 3,5-diphenyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
49. 4-phenylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
50. 4-(4-methylbenzene)sulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
51. 4-butylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
52. 4-propylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
53. 4-ethylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
54. 3,5-dimethyl-4-(N,N-dimethylsulphonamido)-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
55. 4-N-methylsulphamoyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole,
56. 4-sulphonic-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-pyrazole,
57. 1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1-imidazole,
58. 2-methyl-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
59. 4,5-dichloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]-butyl}-1H-imidazole,
60. 4-chloro-1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,

61. 4,5-dichloro-2-methyl-1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]butyl}-1H-imidazole,
62. 4-chloro-1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
63. 4,5-dichloro-2-methyl-1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}-1H-imidazole,
64. 4-chloro-1-{4-[4-(3-methoxyphenyl)-1-piperazinyl]-butyl}-1H-pyrazole,
65. 1-{4-[4-(4-methoxyphenyl)-1-piperazinyl]butyl}pyrrole,
66. 1-{4-[4-(2-methoxyphenyl)-1-piperazinyl]butyl}pyrrole,
67. 1-{4-[4-(phenyl)-1-piperazinyl]butyl}pyrrole,
68. 4-chloro-1-{4-[4-(phenyl)-1-piperazinyl]butyl}-1H-pyrazole,
69. 4,5-dichloro-2-methyl-1-{4-[4-(phenyl)-1-piperazinyl]butyl}-1H-imidazole,
70. 4-chloro-1-{4-[4-(2-chlorophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
71. 4,5-dichloro-2-methyl-1-{4-[4-(2-chlorophenyl)-1-piperazinyl]butyl}-1H-imidazole,
72. 4-chloro-1-{4-[4-(3-chlorophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
73. 4,5-dichloro-2-methyl-1-{4-[4-(2-cyanophenyl)-1-piperazinyl]butyl}-1H-imidazole,
74. 4,5-dichloro-2-methyl-1-{4-[4-(2-fluorophenyl)-1-piperazinyl]butyl}-1H-imidazole,
75. 4-chloro-1-{4-[4-(2-cyanophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
76. 4,5-dichloro-2-methyl-1-{4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl}-1H-imidazole,
77. 4-chloro-1-{4-[4-(3-trifluoromethylphenyl)-1-piperazinyl]butyl}-1H-pyrazole,
78. 4-chloro-1-{4-[4-(2-fluorophenyl)-1-piperazinyl]butyl}-1H-pyrazole,
79. 4-chloro-1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-pyrazole,
80. 4,5-dichloro-2-methyl-1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-imidazole,

81. 1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-1,2,4-triazole,

82. 1-{4-[4-(1,2-benzisothiazol-3-yl)-1-piperazinyl]butyl}-1H-benzimidazole,

83. 4-bromo-1-{4-[4-(5-bromopyrimidin-2-yl)-1-piperazinyl]butyl}-1H-pyrazole,

84. 4-chloro-{4-[4-(5-bromopyrimidin-2-yl)-1-piperazinyl]butyl}-1H-pyrazole.

11. A method according to any one of claims 4-9 wherein said compound is 4-chloro-1-{4-[4-(2-pyrimidinyl)-1-piperazinyl]butyl}-1H-pyrazole dihydrochloride.

12. A method according to claim 4 substantially as hereinbefore described with reference to any of the examples.

DATED : 7 October, 1998

PHILLIPS ORMONDE & FITZPATRICK
Attorneys For:
LABORATORIOS DEL DR. ESTEVE, S.A.